

<b>Sponsor/Sponsor-Investigator</b>	Ente Ospedaliero Cantonale
<b>Study Title:</b>	<i>Can Non Invasive Methods for Fluid Responsive Assessment Optimize Preventive Volemic Repletion in Order to Prevent Significant Hypotension After Spinal Anesthesia? A Randomized Trial.</i>
<b>Short Title/Study ID:</b>	<i>Predict Fluid Responsiveness in Spinal Anesthesia. (CERU-1401)</i>
<b>Protocol Version and Date:</b>	Version 1.8 (24 February 2014)
<b>Trial Registration:</b>	<i>The study is currently registered in the official register of the National Institute of Health (NIH) on the site <a href="http://www.clinicaltrial.gov">www.clinicaltrial.gov</a>, where it is possible consult in detail the design of the clinical trial, the objectives, the criteria of enrollment and statistical study data. The official registration number is NCT02070276 and can be freely consulted starting from the homepage by entering the official register number in the "search" field. The study was further recorded c / o Kofam (Koordinationsstelle Forschung am Mensche) with the protocol number SNCTP000000500.</i>
<b>Study Category with Rationale</b>	<i>Study category: Procedural / Intervention.</i>
<b>Background and Rationale:</b>	<i>Spinal anesthesia is a widely used regional anesthesia technique used in everyday clinical practice. It consists of the injection of a local anesthetic in the dural sac to obtain an anesthetic block in the roots of the local spinal nerves. After spinal anesthesia there is a reduction in vascular resistance systemic, with risk of arterial hypotension; for this later spinal anesthesia appears to be essential to correct the volume status of patient through the administration of fluids - normally infused in empirical manner - possibly associated with the administration of amine, with the aim of increasing peripheral resistance. The purpose of the study is to test the hypothesis that the use of two non-invasive methods before performing a spinal anesthesia, compared with the standard method (empirical volume filling) may reduce the impact of arterial hypotension through adequate filling pre-procedural, avoiding at the same time a water overload. All this with the aim of ensuring the execution of spinal anesthesia in the safest possible way for the patient in clinical practice current.</i>

<b>Objective(s):</b>	<p><i>In clinical practice today the execution of spinal anesthesia is performed without a preliminary study of the volemic status of the patient. The doctor monitors the vital signs stabilizing blood pressure only when the patient manifested signs or symptoms of hemodynamic instability. It is sometimes given empirically a bolus of fluids before and during the procedure, but without knowing the actual volume status of the patient, with potential risks related to fluid overload.</i></p> <p><i>For about ten years, the literature has shown the presence of invasive and non-invasive methods to predict fluid responsiveness based on the assumption of the Frank-Starling curve. Until now, however, have never been applied to such predictive parameters in the setting anesthesia in patients undergoing spinal anesthesia, and then to a procedure predictably at risk of hypotension can potentially be prevented/reduced in frequency and severity with a suitable filling Fluid challenge. Still, in such clinical settings has not been studied the usefulness of non-invasive methods which, although less accurate compared to the analysis of invasive parameters, appear to be useful in the reduction of hypotensive episodes potentially dangerous for the patient.</i></p> <p><i>The aim of this study is to determine whether two non-invasive methods, free from risk, readily reproducible and feasible at the bedside such as ultrasound study of the inferior vena cava and the PLRT may, if implemented systematically before the procedure, drive towards individualized optimization volume status of the patient , which can significantly reduce the incidence of hypotension after spinal anesthesia in adult patients is not critical.</i></p>
<b>Outcome applicable, Basisformular):</b> (if see Primary Outcome Secondary Outcome	<p><i>The primary objective is to quantify cases of arterial hypotension that come to occur following spinal anesthesia, comparing i patients brought to euolemia according to the TTE and PLRT parameters compared to patients treated according to the current standard. For arterial hypotension, in accordance with the international standard definitions, a drop is defined of systolic blood pressure over 50 mmHg compared to conditions basal, an absolute systolic pressure value of less than 80 mmHg, an average arterial pressure below 60 mmHg or one clinically symptomatic hypotension (dizziness, pallor, sweating, nausea).</i></p> <p><i>The first secondary objective is to stratify the rate of hypotension in the three groups based on further variables (age over 60 years, recruitment) of antihypertensive therapy, ASA classification, patient position post-operative) to see if the effects are more visible in a specific population.</i></p> <p><i>A further secondary objective is to quantify the water supply between the three comparison groups, using the patients of the control group as a reference, to be able to assess whether filling techniques, titrates on echocardiographic and / or evaluation response to internal mobilization of liquids is associated with a less unnecessary administration of liquids.</i></p>
<b>Study Design, Basisformular):</b> (if see	<p><i>Primary purpose: Prevention</i>  <i>Study phase: N / A</i>  <i>Intervention model: Parallel Arms</i>  <i>Number of arms: 3</i>  <i>Masking: Single Blind</i>  <i>Allocation: Randomized</i>  <i>Endpoint Classification: N / A</i>  <i>Enrollment: 380 [Anticipated]</i></p>

<b>Inclusion/Exclusion Criteria, see Basisformular:</b>	<p><i>3.1 Inclusion criteria</i>  <i>Non-critical adult patients,</i>  <i>Patients with loco-regional anesthesia with spinal technique</i>  <i>Patients in the election regime</i>  <i>Patients classified as ASA I, ASA II and ASA III</i></p> <p><i>3.2 Exclusion criteria</i>  <i>Patients already equipped or requesting blood pressure monitoring invasive (arterial catheter, Swann-Ganz catheter, catheter of Peak)</i>  <i>Patients with pre-procedural hypotension, defined as finding in two consecutive measurements of PAs less than 80 mmHg or PAm 60 mmHg</i>  <i>Patients unable to give their informed consent for communication difficulties due to language barriers or processes congenital / acquired determining mental retardation or one any reduction in one's ability to understand or want to be able to give your informed consent to the study</i>  <i>Patients in whom anesthesia is not possible spinal due to patient's refusal, due to technical difficulties in collecting,</i>  <i>for pathological clinical conditions determining a high risk of peri-procedural complications.</i>  <i>Patients with INR&gt; 1.5 and / or aPTT in therapeutic range (understood as value over 1.5-2 times the patient's normal values), anti-activity Xa in therapeutic range.</i>  <i>Patients with severe thrombocytopenia (&lt;50 G / l)</i></p>
<b>Measurements and Procedures:</b>	<p><i>Randomized three-arm interventional study involving the enrollment of all non-critical patients who undergo spinal anesthesia for any clinical indication in our Service. The anesthetic choice of loco-regional anesthesia is decided by the anesthesiologists in the pre-assessment of the patient according to the current clinical practice, according to the type of operation and the patient's current clinical conditions.</i></p>
<b>Study Product/Intervention according to KlinV, if applicable:</b>	<p><i>Arm B</i>  <i>Before performing spinal anesthesia as in arm A (considered the control arm) a trans-thoracic echocardiography is performed in order to assess the patient's volume status. If it is responsive to liquids, a standard 500 ml infusion is given. The procedure is repeated until the patient is no longer responsive to liquids; at this point we proceed with spinal anesthesia.</i></p> <p><i>Arm C</i>  <i>Before performing spinal anesthesia as in arm A (considered the control arm) what is called Passive Leg Raising Test (PLRT) is performed: in a passive manner the position of the bed is changed so as to bring the trunk from 45 ° at 0 ° and the legs consequently rising from 0 ° to 45 °. Some hemodynamic parameters are measured (arterial pressure, heart rate, etCO2): if the values increase by 5% the patient is considered responsive to liquids and a standard infusion of 500 ml of crystalloids is administered. The procedure is repeated until the patient is no longer responsive to liquids: at this point we proceed with spinal anesthesia.</i></p>

<b>Comparator(s) (if applicable):</b>	Arm A <i>The current clinical standard for spinal anesthesia is considered; it is used as a control and statistical reference sample. Before anesthesia the patient is equipped to measure arterial pressure, the ECG, a peripheral venous route and a peripheral saturimetry are positioned. The blood pressure control is set as standard every 5 minutes until the spinal anesthesia procedure; the pressure sleeve is placed on the upper arm during spinal anesthesia. The patient's data and vital signs are recorded and an infusion of crystalloids (NaCl 0.9% or Ringer-acetate) is given with the administration of 500 ml during the whole procedure from arrival to "induction place" until the start of the surgical operation .</i>
<b>Number of Participants with Rationale (if no Power Analysis conducted):</b>	<i>A sample of 288 patients appears adequate to obtain a confidence interval of 0.95. Assuming an exclusion and loss rate at the follow-up of 30% total, it is estimated necessary to include 370 patients (maximum error = 0.05, value of z = 1.96).</i>
<b>Study Duration:</b>	<i>One year from enrollment of the first patient until the expected number of participants is reached. Maximum duration 12 months.</i>
<b>Study Schedule:</b>	<i>Start of study: 1 June 2014  Study deadline: 31 May 2015</i>
<b>Investigator(s):</b>	<i>Dr. med. Samuele Ceruti (Principal Investigator) Capoclinica Medicina Intensiva EOC  Dr. med. Luciano Anselmi (Study Coordinator) Primario Anestesia EOC  <b>Ospedale Regionale di Bellinzona e Valli Servizio di Anestesia Via Ospedale 12 6500 – Bellinzona 091/811.91.11</b></i>
<b>Study Centre(s):</b>	<i>Single-center study</i>

<b>Statistical Analysis incl. Power Analysis</b>	<p><i>Power analysis:</i> The study power calculation was performed, considering a 25% reduction in the incidence of arterial hypotension after spinal anesthesia with each of the methods compared to the control group, consisting of patients subjected to unguided filling.</p> <p><i>Statistic analysis</i> A randomization program will assign patients to one of the 3 arms of the study, assigning a code to the patient. The data will be initially collected on paper forms by researchers not involved in the randomization process. The data will then be transferred to an IT database and anonymized, so that the researcher performing the statistical analysis is blinded to the assignment arm.</p> <p>The results will be subjected to statistical analysis using the Student test for continuous variables with normal distribution, the Mann-Whitney test for non-normal distribution variables and the Chi-square test for dichotomous variables. A value of <math>p &lt; 0.05</math> will be assumed to be significant.</p>
<b>GCP Statement:</b>	<p>The study is conducted in accordance with the written protocol, the Helsinki declaration, international GCPs and national and local legal regulations.</p>

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**Study Procedure/Flowchart with Timelines: Study specific Examinations have to be clearly identified**

June 1, 2014: enrollment begins

March 31, 2015: enrollment deadline (estimated)

May 31, 2015: protocol closure (estimated)

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**Risks/ Inconveniences, which are Study specific:**

*To reduce the risk of exposing the patient to hypotensive episodes or excessive water overload, patients who were truly or potentially unstable were excluded, patients with cardiovascular diseases considered to be severe according to the classification of the American Society of Anesthesiology (from ASA IV level included in then) and patients with mechanical ventilation.*

*The methods used (TTE and PLRT) appear completely non-invasive and free of side effects<sup>12</sup>.*

*The study therefore does not use drugs or experimental procedures and does not investigate a population at risk. On the contrary, it simply aims to compare the current clinical practice with two different protocols that use safe methods and without side effects, to minimize the risks of the same for patients: replace an empirical volume filling with a targeted and personalized based on the state patient volume.*

**Coverage of Damages: Insurance (yes/no)? Sum?**

No

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**Storage of Data-and Samples for Future Research Aims: yes/no?,**

No

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**Ethical Considerations:**

*If the study proves to be able to show statistical significance, it will be possible to perform the spinal anesthesia procedure more safely for the patient in terms of: a) lower rate of arterial hypotension, b) adequate fluid loading.*

*It will also be possible to extend a future study (designed in a similar way) to more complex groups of patients, where the avoidance of arterial hypotension and excessive water overload can have a decidedly greater and more significant prognostic impact.*

*It will also be possible to lay the foundations for evaluating new mini / non-invasive methods for assessing the patient's water status before the spinal anesthesia procedure (or even other similar procedures) in the future, always with the aim of reducing peri-procedural risks .*

*The study is risk free as explained in the previous section on "study risks".*

*The strengths of the methodology are:*

- a) stratified randomization: the three study groups are randomized and adequately balanced for parameters such as age, ASA risk class, taking anti-hypertensive therapy.*
- b) Early publication of the protocol: for the FDA (on the website [www.clinicaltrials.gov](http://www.clinicaltrials.gov)) and for the Swiss Federation (on the website [www.kofam.ch](http://www.kofam.ch)) the protocol is published before the start of enrollment. The study design is established first and not adapted to the results found, in order to be able to demonstrate the results with absolute significance, regardless of their value.*
- c) Patients' progressiveness: patients will not be pre-selected for the purpose of adapting the protocol to the "best" patients for the study. All patients with all the features present in the inclusion criteria will be enrolled, without a rationalized choice a priori or a posteriori (subject to the exclusion criteria).*

- d) *Safety for participants: it was decided to restrict the study as much as possible by focusing on a population of patients at low risk of complications in the event of arterial hypotension and / or water overload, in order to evaluate the usefulness of the procedures totally canceling the risks for patients.*
- e) *Single-Blinding: after the randomization phase, the patient's documents are totally anonymised and blinded to the type of study arm. It will therefore be possible to perform an analysis of the data in a completely separate and independent manner from the knowledge of the branch of belonging during the protocol.*
- f) *Per-protocol analysis / intention to treat: the data will be analyzed both globally and further by focusing on the patients actually studied as per protocol, without any element of lack of adherence. It will therefore be feasible to evaluate the rate of adherence to the protocol (with the possibility of determining the feasibility on the part of third parties) and the double analysis of patients actually studied as per protocol.*

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**The most relevant References:**

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